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TITLE: Treatment of Vestibular Dysfunction Using a Portable Stimulator

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CONTRACTING ORGANIZATION: Veterans Biomedical Research Institute
East Orange, NJ 07018

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14. ABSTRACT 59 participants have been enrolled in this research study. 33 subjects have been found to have hypofunction.					
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1. INTRODUCTION

Vestibular symptoms seem to be a common problem with ~20% of veterans complaining of dizziness and those with dizziness demonstrating increased risk of Motor Vehicle Accidents. To treat veterans with vestibular dysfunction we will optimize stimulation using a portable stochastic noise electrical stimulator and determine the effectiveness of subsensory electrical stimulation in a population of veterans with verified impaired vestibular function. We will perform experimental and sham stimulation on patients with impaired function to improve clinical vestibular and balance function during testing. We will assess the effectiveness of using this portable stochastic noise electrical stimulator to improve driving performance and determine what effect subsensory electrical stimulation has on vestibular function.

2. KEYWORDS

None to report

3. ACCOMPLISHMENTS

Major Goals of the Project

Major Goal 1 - Develop a portable stimulator which can be worn continuously and used to improve vestibular function (April 2014 to June 2016)

Subtask 1: Establish Project Management System/Develop Logistical Plan (April – Aug 2014)

- a. Train the current members of the team (research assistant and research engineer) on vestibular screenings, balance assessments, and electronic stimulation
- b. Research engineer will optimize equipment and write analysis scripts for aim 1

Milestone #1: Establish project management system, hire and train research staff (Planned Completion Aug 2014) – Completed April 30, 2014

Subtask 2: Regulatory Review and Approval Process (April – Sept, 2014)

- a. Finalize IRB paperwork including application, protocol and consent form
(Completed)
- b. Submit any revisions requested by the regulatory board prior to approval
(Completed)
- c. Obtaining DoD HRPO approval
(Completed)

Milestone #2: Regulatory review and approval obtained (Planned Completion Nov 2014) – 100% complete

Subtask 3: Recruitment Plan (Sept 2014 – Jan 2015)

- a. Develop plan to meet recruitment goals **(Completed)**

- b. Mail IRB approved recruitment letters to Veterans seen at the WRIISC; follow up with phone calls
 - ~229 Veterans evaluated at the WRIISC screened positive for dizziness – 25 letters per week will be mailed to this subset followed by a phone call
(A total of 385 veterans have been contacted by phone to participate in the study, with 140 interested in participating and 92 eligible for study visits)
- c. Distribute flyers to all VA facilities and their ambulatory services including community-based outpatient clinics to publicize the study
- d. Work with NJ VA Physical Medicine & Rehabilitation Department (TBI clinic) to recruit from their patient population
- e. Contact Veteran Service Organizations for support on best way to perform outreach
(Completed)

**Milestone #3: Recruitment Plan Executed (Planned Completion Jan 2015)
 – 70% Completion**

Subtask 4: Development of Portable Stimulator (April 2014 – March 2016)

- a. PI to meet with Dr. Breen at University of Western Sydney to go over specifications for Portable Stimulator Design **(Completed)**
- b. Development of initial prototype design at University of Western Sydney **(Completed)**
- c. Production of first generation prototype portable stimulator at University of Western Sydney to be shipped to New Jersey for testing **(Completed)**
- d. Redesign of prototype unit at University of Western Sydney based on findings from experiments performed in New Jersey **(Completed)**
- e. Production of second generation prototype vestibular stimulators at the University of Western Sydney for further testing in New Jersey **(In Process)**
- f. Redesign of prototype unit at the at University of Western Sydney based on findings from experiments performed in New Jersey
- g. Production of third generation prototype vestibular stimulators at the at University of Western Sydney for shipping to New Jersey for further testing
- h. Redesign of third generation stimulators for fabrication of units for use in Specific Aim 2 performed at National University of Ireland Galway
- i. Fabrication of 20 units based on final design specifications at the National University of Ireland Galway
- j. Testing of initial fabricated units from the National University of Ireland Galway in New Jersey to ensure they are meeting required standards and creating desired improvement
- k. Shipment of remaining units from National University of Ireland Galway to New Jersey for use in Specific Aim 2

**Milestone #4: 20 portable stimulators received (Planned Completion March 2016)
 – 50% Completion**

Subtask 5: Enroll subjects and conduct testing on Sub-sensory Galvanic Stimulation Study (Oct 2014 – June 2016)

- a. Screen subjects/ collect data: total of 250 subjects
 - 3 subjects per week/ 3 study visits (3 hours each)

- Vestibular testing, balance assessments
(63 subjects have been enrolled and completed study screening visit, 18 have completed experimental trial out of 42 planned, and another 16 have been screened as having low otolith function and are being scheduled for experimental trials. Therefore we are at 34/42 necessary scheduled.)
 - b. Data analysis (Post-doctoral fellow/research assistant will continually analyze data as collected) **(In Process)**
 - c. Biomedical engineer will continue to modify equipment and MATLAB analysis scripts as needed
 - d. Present/publish work
- Milestone #5: Enrolled and tested subjects (Planned Completion April 2016) – 38% 16/42 Complete**
- Milestone #6: Data analysis completed (Planned Completion May 2016) –38% 16/42 Complete**
- Milestone #7: Data presented/published (Planned Completion June 2016) – 0% Completion**

Major Goal 2 – To examine long term improvement of vestibular function in veterans with electrical stimulation (April 2016 to March 2017)

Subtask 1: Examine effects of Stochastic Noise Over a 6 Week Stimulation Paradigm (April 2016 – April 2017)

- a. Screen subjects/collect data: total of 69 subjects
 - 3 unique subjects per week
 - Subjects return every 3 weeks for balance/vestibular testing
 - Subjects to wear portable stimulator over 6 week trial
 - b. Data analysis
 - Analysis will be performed throughout data collection
 - c. Present/publish work
- Milestone #8: Enrolled and tested subjects (Planned Completion Jan 2017) – 0% Completion**
- Milestone #9: Data analysis completed (Planned Completion Feb 2017) – 0% Completion**
- Milestone #10: Data presented/published (Planned Completion March 2017) – 0% Completion**

Major Goal 3 – To improve driving performance using Electrical Stimulation

Subtask 1: Effect of Improving Vestibular Ocular Reflex on Driving Function (Sept 2016 to March 2018)

- a. Initial testing and safety verification previously completed on driving simulator
- b. Institutional approvals obtained
- c. Pilot motion profiles to obtain optimal motion profiles to test role of vestibular function in driving performance

- d. Engineer will write analysis scripts to measure reaction time, stopping time and trajectory, collision avoidance and emergency braking for driving simulator to measure driving performance
- e. Engineer will develop analysis system which will track acceleration of participant and eye movements to obtain vestibular ocular reflexes while performing driving task
- f. Screen subjects/collect data: total of 69 subjects
 - 3 subjects per week
 - Complete driving simulator protocol (sham and stimulator trials)
- g. Data analysis
- h. Present/publish work

Milestone #11: Testing and safety confirmed (Planned Completion Sept 2016)

– 0% Completion

Milestone #12: IRB approval obtained (Planned Completion Dec 2016)

– 0% Completion

Milestone #13: Pilot testing completed (Planned Completion Feb 2017)

– 0% Completion

Milestone #14: Data collection completed (Planned Completion Sept 2017)

– 0% Completion

Milestone #15: Data analysis completed (Planned Completion Oct 2017)

– 0% Completion

Milestone #16: Data presented/published (Planned Completion March 2018)

– 0% Completion

ACCOMPLISHMENTS DURING THIS ANNUAL PERIOD

Major Activities

Regulatory Review and Approval Process

- a. Obtained IRB approval from the VA which included changes to protocol and adding collaborators to the study

Major Goal 1

Subtask 3: Recruitment Plan

- a. A total of 385 veterans have been contacted by phone to participate in the study, with 140 interested in participating and 92 eligible for study visits.
- b. 63 veterans came in for the screening visit. 34 of those veterans returned for the second visit. 18 completed the study.

Milestone #2: Regulatory review and approval obtained (Planned Completion Date Nov 28, 2014) – 100% complete

Development of Portable Stimulator

- a. Went to University of Western Sydney to work with Dr. Breen on desktop prototype. Designed improved desktop version with improved stimulation characteristics.
- b. Produced several copies of the first generation desktop prototype in NJ for testing on Veterans once HRPO approval is received.
- c. Dr. Breen is working on portable version of desktop stimulator.

Milestone #4: 20 portable stimulators received (Planned Completion March 2016)

– 50% Completion

- 63 subjects have been enrolled into the study and have completed the study screening visit
- Screening visits of 60 subjects have been fully analyzed for eligibility for stimulation visits
- 34 subjects are eligible to return for stimulation visits
- 18 subjects have completed stimulation testing

Specific Objectives for Year 2

- 1) Continued execution of recruitment plan by phone calls, posting flyers, and recruiting from VA TBI patient populations
- 2) Continued enrollment of subjects and data collection
- 3) Analysis of collected data
- 4) Redesign of portable stimulator based on experimental findings and initial plans for miniaturization of stimulator circuit
- 5) Fabrication of 20 portable stimulator units based on final design specifications
- 6) Continue testing using sub-sensory stimulation and analysis of data
- 7) Specific Aim 2: Examine effects of stochastic noise over a 6 week stimulation paradigm

Significant Results of Year 2

- 1) Research flyers have been posted to aid in recruitment. Forty-nine additional people were contacted to participate in this study with 29 people performing a phone screen.
- 2) Of the 132 phone screens, 88 were eligible to participate in the study. 63 participants came in for screening visits during this year making our total enrollment number to 63.
- 3) Overall, we have been able to analyze the screening visits of 60 participants. Of these, 34 show vestibular hypofunction and were/are able to participate in visits using stochastic noise.
- 4) Dr. Breen has miniaturized the circuit and is producing portable stimulators for testing in New Jersey.
- 5) Fabrication of multiple portable stimulators will begin once final designs have been tested.
- 6) A total of 18 subjects have completed stimulation visits and we are in the process of analyzing these results. Data collection using sub-sensory stimulation continues to progress.

- 7) Now that we have identified over 50% of the required number of Veterans with vestibular hypofunction to be test in Aim 1 we have begun the process of submitting the IRB for Aim 2. While slightly behind due to the delay in starting Aim 1 we are confident we will make up ground in year 2.

Major Findings, Developments, Conclusions, and Other Achievements

- There are several findings that are developing out of the initial data. We have found that there has been a significantly greater level of vestibular hypofunction than we originally anticipated. Figure 1 demonstrates the subjects screened up to year 2 and the associated ocular torsion.

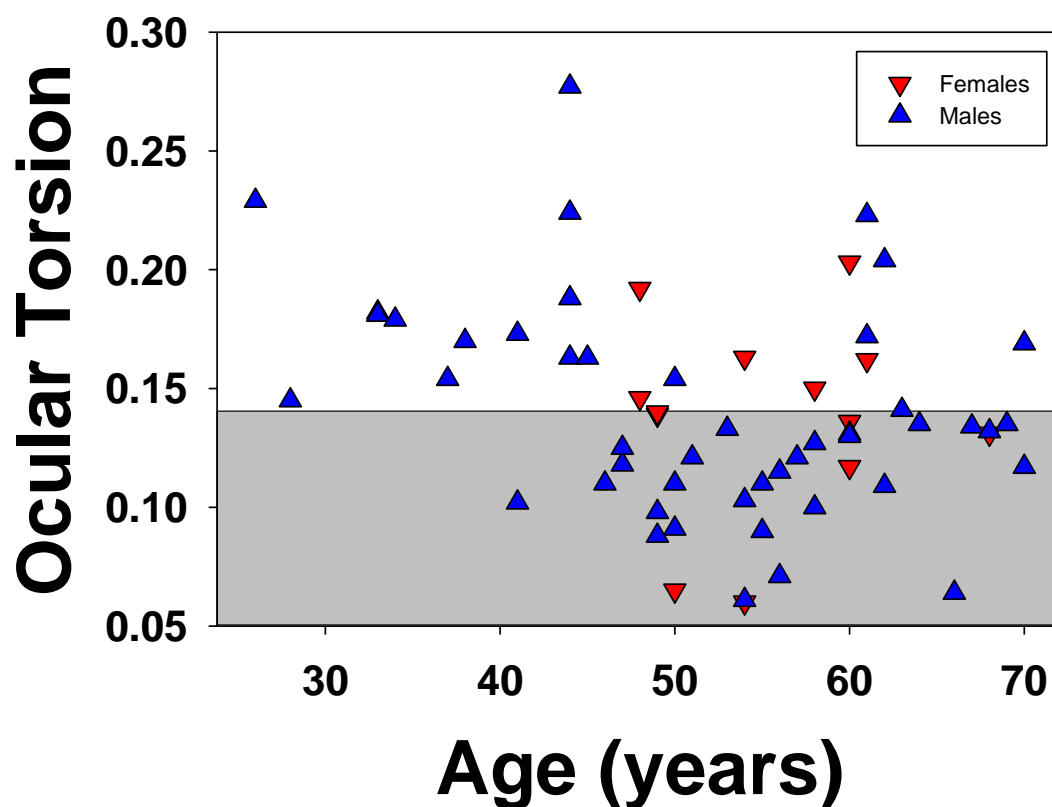


Figure 1 – Ocular torsion of veterans screened as part of Specific Aim 1. Gray box indicates veterans with low otolith function. Veterans recruited into the study have a significantly lower level of vestibular function than expected suggesting this problem may be more prevalent than originally anticipated.

- Comparing the veteran data to a group of civilians of similar age that were part of a previous study the PI completed in Boston we see that the veterans have significantly lower levels of ocular torsion (Figure 2). In fact the mean values in the female and male veterans were 0.14, compared to 0.20 in the female civilians and 0.17 in the male civilians. These data also indicate that female veterans may be at greater risk for vestibular hypofunction. Although larger numbers are needed to confirm this.

Comparison of Ocular Torsion in Veterans vs Civilians

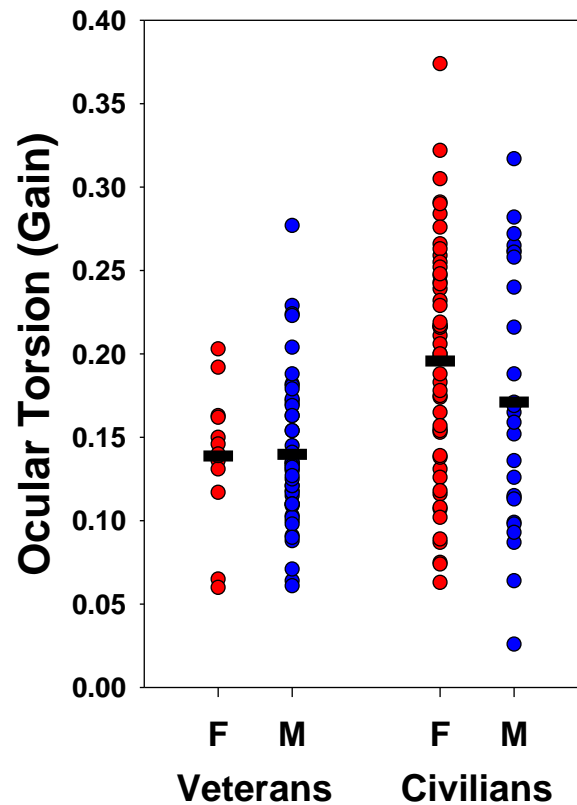


Figure 2 – Ocular torsion in veterans (left) vs civilians (right) of similar age. Note that the veterans have significantly lower ocular torsion than the civilians. These data suggest that veterans may be at risk for vestibular hypofunction. A larger epidemiologic study is necessary to confirm these findings.

- We also examined the effect of the stimulator (V1) on ocular torsion and balance function. We stimulated the veterans using a low level (subsensory) of random electrical noise with 95% of the power banded below 2 Hz. Stimulation levels were set for each individual to cause the greatest increase in their vestibular ocular reflex. Stimulation levels varied but were below 1 mA and were a mean of ± 0.3 mA. Examining ocular torsion we found that in our initial group of 13 veterans with complete data sets, that 10 of 12 males showed an increase during stimulation while 0 of 1 females showed an increase. Even in this small group there was a highly significant mean 16.5% increase with use of the stimulator ($P < 0.001$).

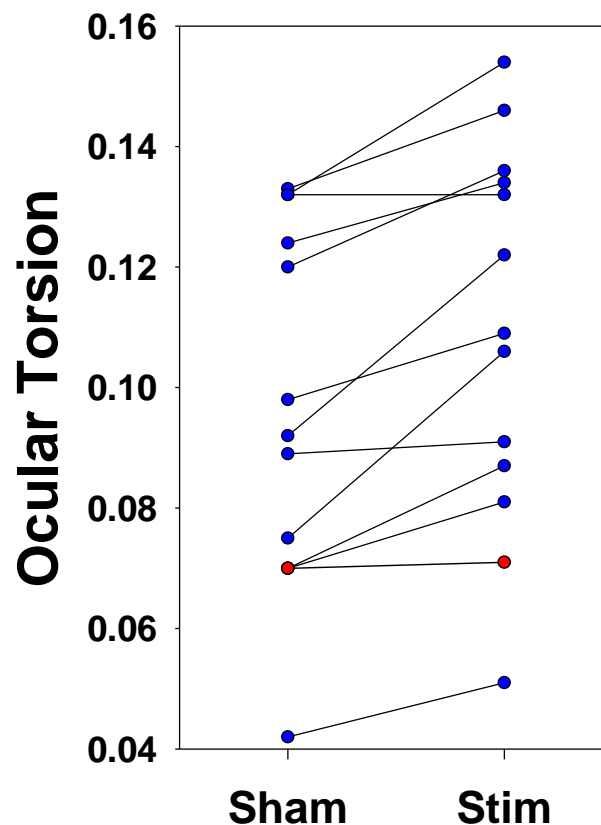


Figure 3 – Increase in ocular torsion during sub sensory levels of random electrical noise applied at the ear lobe.

- We further examined the balance of individuals during sham and stim sessions at the levels used above to produce an increase in ocular torsion. Our goal was to determine if the improvement in vestibular ocular reflex would translate into an improvement in balance function. Examining the response we found that the results were not clear. Figure 4 demonstrates the response when comparing a sham stim trial (C) to the stim trial in which subsensory levels of random electrical noise were applied to the ears. What we found was that changes were not as consistent as seen with the ocular torsion. Some subjects improved while others appeared to do worse. The response was also dependent

on the condition. So during eyes open on a fixed surface, no trend can be seen. To our surprise, during the eyes closed condition there also was not a consistent trend. While 6 of the 14 subjects appeared to improve (sway reduced), the rest tended to increase. We had expected that improved vestibular function in this group should result in improved balance function with eyes closed since they would rely more heavily on vestibular information. Examining their balance during the conditions in which they were standing on an unstable surface, providing a greater challenge and making them rely more heavily on vestibular function, we again got surprising results. During the condition with eyes open where they could use both vision and vestibular inputs there was a trend towards reduced sway with 11 of 14 improving. In contrast with eyes closed, 12 of 14 showed greater sway suggesting the stimulation was not improving their balance.

- These data highlight that prior to long term stimulation we may need to examine the adaptation of the individuals to the stimulation. One possible explanation for the differing response is that when vestibular function is improved immediately with the stimulation, during a very difficult balance task (ECF - eyes closed on unstable surface) the brain is not able to fully integrate the new information. If given more time, the balance system will reweight the sensory inputs to more effectively use the improved vestibular function. Further work is necessary to see if this is true. We plan to consider adding a short term

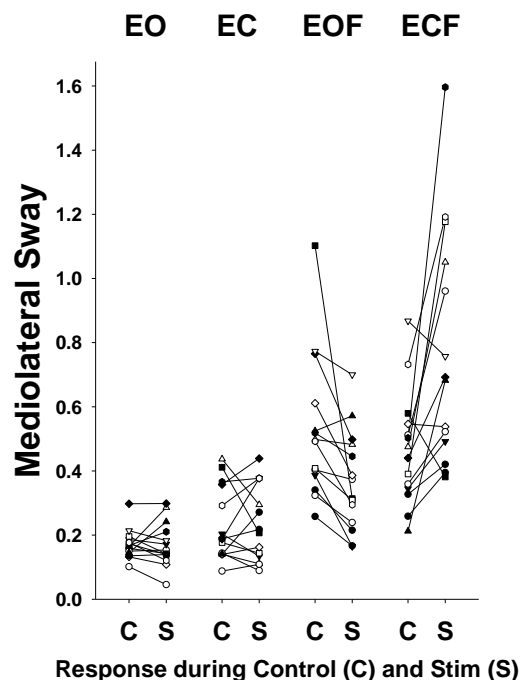


Figure 4 – Response of 14 veterans to Control (no stim) and low level random electrical stimulation (S) while performing a 30 sec static standing balance task on a force plate under four conditions: Eyes open on firm surface (EO), eyes closed on firm surface (EC), eyes open on unstable surface consisting of foam block (EOF), eyes closed on unstable surface (ECF). Traditionally it is assumed that vestibular function is more important during the trials with eyes closed, so EC and ECF. However, stimulation that improved vestibular ocular reflex did not seem to reduce sway consistently during these trials. However, sway during EOF did improve suggesting the improved vestibular input may have bolstered the sensory integration with vision to improve balance.

one week study before attempting the 12 week trial

What opportunities for training and professional development has the project provided?

This project has provided training for all research staff to be competent at vestibular screenings, balance assessments, and electronic stimulation procedures. The post-doctoral fellow has been able to travel to Dr. Schubert's clinic at Johns Hopkins to be trained on most up to date vestibular testing techniques. Biomedical engineer has been able to develop improved stimulator prototype under guidance of Dr. Breen. All staff travelled to Dr. Wood's lab to be trained on vestibular testing.

How were the results disseminated to communities of interest?

- Nothing to Report

What do you plan to do during the next reporting period to accomplish the goals?

- 1) Continued execution of recruitment plan by phone calls, posting flyers, and recruiting from VA patient populations
- 2) Enrollment of subjects and data collection
- 3) Analysis of collected data
- 4) Test miniaturized units produced by Dr. Breen in lab to ensure they are ready for use in Specific Aim 2.
- 5) Continue testing using sub-sensory stimulation
- 6) Analysis of sub-sensory stimulation data
- 7) Begin process of gaining IRB approval for Specific Aim 2.
- 8) Develop driving simulator protocol for Specific Aim 3.

4. IMPACT

What was the impact on the development of the principal discipline(s) of the project?

- Nothing to Report

What was the impact on other disciplines?

- Nothing to Report

What was the impact on technology transfer?

- Nothing to Report

What was the impact on society beyond science and technology?

- Nothing to Report

5. CHANGES/PROBLEMS

- Nothing to Report

Changes in approach and reasons for change

- Nothing to Report

Actual or anticipated problems or delays and actions or plans to resolve them

- With the 9 month delay in study approval, our recruitment numbers are lower than estimated. We are reporting an unexpectedly high level of vestibular hypofunction within our population (56%) from analysis of our initial 56 subjects. If this level of hypofunction within our population persists it would significantly alter the number of subjects required to reach statistical significance within our study. At the current rate, 75 would need to be enrolled to find 42 with hypofunction. Based on this preliminary finding, we believe that we will be able to reach our goals by July 2016, 3 months behind our original schedule. We will continue to review our recruitment success and analysis in the next yearly report.
- Stimulator development has progressed but not as quickly as originally hoped. Stimulator prototype 2 failed due to a conflict between power converters for the digital control stage and the analogue output stage. All other elements of prototype 2 were successful. Stimulator prototype 3 was constructed with an alternate analogue output stage power converter. A fully functional prototype 3 model is now constructed and bench tested successfully. Minor software and hardware modifications are now being finalized to realize the production version. Full production will commence following sign-off and pilot test of the stimulator. A full suite of units can be produced and shipped within two months from that point.

Changes that had a significant impact on expenditures

- There were no changes in expenditures.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents:

Significant changes in use or care of human subjects

- No changes to use of care of human subjects to report

Significant changes in use or care of vertebrate animals.

- No animal use research will be performed to complete the Statement of Work

Significant changes in use of biohazards and/or select agents

- No biohazards and/or select agents will be used to complete the Statement of Work

6. PRODUCTS**Publications, conference papers, and presentations**

- J. Michalik, K. Migdal, J. Serrador. "Comparison of Subjective Perception of Balance to Ocular Counter Roll" Experimental Biology 2016, San Diego, CA
- Haber Y, Fox A, Samy B, Obatusin M, Chandler H, Wood S, Serrador J. "Prolonged Slow Phase Velocity Decay Time Constant is Associated with Worse Canal Function in Veterans with PTSD." 38th Annual Mid-Winter Meeting for Association for Research in Otolaryngology. Baltimore, MD, 2015.
-

Journal publications.

- Nothing to Report

Books or other non-periodical, one-time publications

- Nothing to Report

Other publications, conference papers, and presentations.

- Nothing to Report

Website(s) or other Internet site(s)

- Nothing to Report

Technologies or techniques

- Nothing to Report

Inventions, patent applications, and/or licenses

- Nothing to Report

Other Products

- Nothing to Report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**What individuals have worked on the project?**

Name: Jorge Serrador, PhD

Project Role: PI

Nearest person month worked: 2.5

Contribution to Project: no change

Name: Apollonia Fox, PhD

Project Role: Postdoctoral Fellow

Nearest person month worked: 1.5

Contribution to project: No change

Name: Mosadoluwa Obatusin, MEng

Project Role: Research Assistant

Nearest person month worked: 3

Contribution to Project: no change

Name: Bishoy Samy, MS

Project Role: Research Engineer

Nearest person month worked: 3

Contribution to Project: no change

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

- Nothing to Report

What other organizations were involved as partners?

1. Organization Name: University of Western Sydney- Paul Breen, PhD

Location of Organization: Australia

Partner's contribution to the project:

- Financial support – Nothing to report
- In-kind support – Dr. Breen's salary is covered by UWS as detailed in original proposal.
- Facilities – Nothing to report
- Collaboration – Designed a novel low power stochastic noise stimulator that will be used to improve vestibular function in our patients
- Personnel exchanges – Nothing to report
- Other – Nothing to report

2. Organization Name: National University of Ireland Galway- Gearóid Ó Laighin, PhD

Location of Organization: Ireland

Partner's contribution to the project:

- Financial support – Nothing to report
- In-kind support – Prof. Ó Laighin's salary is covered by NUIG as detailed in original proposal.
- Facilities – Nothing to report
- Collaboration – Assist Paul Breen in the design of a novel low power stochastic noise stimulator
- Personnel exchanges – Nothing to report
- Other – Nothing to report

3. Organization Name: Azusa Pacific University- Scott Wood, PhD

Location of Organization: California

Partner's contribution to the project:

- Financial support – Nothing to report
- In-kind support – Nothing to report
- Facilities – Nothing to report
- Collaboration – Provided expertise in scientific protocol development specifically with regards to driving performance assessment
- Personnel exchanges – Nothing to report
- Other – Nothing to report

4. Organization Name: John Hopkins University- Michael Schubert, PhD

Location of Organization: Maryland

Partner's contribution to the project:

- Financial support – Nothing to report
- In-kind support – Nothing to report
- Facilities – Nothing to report
- Collaboration – Provided expertise in scientific protocol development specifically with regards to vestibular assessment
- Personnel exchanges – Nothing to report

- Other – Nothing to report

8. SPECIAL REPORTING REQUIREMENTS

- None

QUAD CHARTS: If applicable, the Quad Chart (available on <https://www.usamraa.army.mil>) should be updated and submitted with attachments.

9. APPENDICES: None.